UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

MU

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,338	02/08/2002	Cecilia Anders	P31731X1C1	2718

7590 02/17/2004

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939

EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,338	ANDERS ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37 and 45-49* is/are pending in the application.

4a) Of the above claim(s) *1-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-36 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/018,806.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/8/02 (1 page)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on November 10, 2003), Applicants filed a response received on December 11, 2003. Thus, Claims 1-37 and 45-49 are pending in the instant Office action.

Election

2. Applicants' election of Group XVI, Claims 30-36 and 45-49, in a paper received on December 11, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

Claims 1-37 45-49 are pending in the instant application. Claims 1-29 and 37 are withdrawn from consideration as non-elected inventions. Claims 30-36 and 45-49 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the foreign application 9702218.0 filed on February 4, 1997 filed in the United Kingdom as requested in the declaration. A certified copy of the foreign priority document, in English, has been filed with the Office in the parent application 09/018,806. The instant application is also granted the benefit of U.S. application 09/018,806 filed on February 4, 1998, now abandoned, as requested in the transmittal sheet and in the first lines of the specification.

Information Disclosure Statement

4. The information disclosure statement filed on February 8, 2002 (a single page) has been reviewed, and most of its references have been considered as shown by the Examiner's initials next to each citation on the attached copy. No copy of the King *et al.* reference could be found in the parent; for consideration of this reference, Applicants must file the appropriate copy.

Applicants also filed inappropriate pages, including a copy of a PTO-892 and a copy of a signed 1449 from previous prosecution with numerous markings. None of these have space for the Examiner's initials upon consideration, and the previously signed 1449 is not legible as to which items are to be considered. These inappropriate pages have not been considered because they are not an acceptable citation of documents considered to be relevant (see M.P.E.P. § 609). If Applicants would like this documents considered, Applicants must cite them on an appropriate information disclosure statement for consideration by the Examiner.

Declaration

5. The declaration, filed along with the instant application, is a copy of a declaration for PCT/EP98/00644 filed on February 4, 1998 as noted on page 1 of the declaration; this application is identical to U.S. 09/018,806, the continuation parent case as noted in the transmittal. Said declaration in the instant application is sufficient.

Compliance with the Sequence Rules

6. By virtue of the request on the transmittal sheet of the instant application, the computer readable form (CRF) of the sequence listing from the parent application 09/018,806 has been copied and is the official CRF for the instant application. However, the statement that the CRF

and the paper copies of the sequence listing are the same does not clearly note that it is the CRF transferred from the parent 09/018,806 and the separately filed paper copy that are the same; such a statement is required.

7. The instant application does not fully comply with the sequence rules because amino acid sequences in Figures 1A-1P are disclosed without benefit of SEQ ID NO; these sequences are noted on page 12. Applicants must describe these sequences either directly in the Drawings or in the Brief Description of the Drawings by SEQ ID NO.

Objections to the Specification

8. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Isolated Clavulanic Acid Obtainable from Fermentation of Modified *Streptomyces*---

9. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the full name of the source species of the genes that are manipulated, *Streptomyces clavuligerus,* as well as description of the purified form of clavulanic acid produced thereby, for completeness.

10. The specification is objected to for lacking updated continuity data in the first paragraph. The instant application claims the benefit of U.S. non-Provisional Application No. 09/018,806

filed on February 4, 1998, now abandoned. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

11. The specification is objected to for containing pages 13-29 that contain figures that must be deleted; said figures are found in the separately filed drawings.

12. The specification is objected to for omitting a Brief Description of the Drawings. Said description must describe Figure 1A-1P and must describe the amino acid sequences disclosed therein by SEQ ID NOs (the DNA sequence is noted in Figure 1A as being SEQ ID NO:1).

13. The specification is objected to for being confusing with respect to the sequence listing. The sequence listing contains 19 sequences. Every SEQ ID NO is mentioned in the specification and/or the claims except SEQ ID NOs: 8-19. It is unclear why said sequences are in the sequence listing if they are not described in the specification. All SEQ ID NOs in the sequence listing must be described in the specification. Appropriate correction is required.

Claim Objections

14. Claims 30-32 and 35-36 are objected to for depending from non-elected Claims 25, 15, and 1. Claim 30 must be rewritten as an independent claim to incorporate all the limitations of Claims 1, 15, and 25. Correction is required.

15. Claim 45 is objected to for a typographical error. The term "alenyl" should be ---alanyl---as found throughout the specification. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 30-32 and 35-36 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) In Claim 1, genes that are "specific for 5S clavam biosynthesis in *S. clavuligerus*" that are "not essential for 5R clavam biosynthesis" are unclear. The specification teaches 6 genes in this "category", which genes can be included. However, the term "specific for" does not clearly define the association the genes must have with 5S (not 5R) clavam biosynthesis.
b) In Claim 15, the process steps are unclear since they seem to include "manipulation" and "its inclusion". Is the DNA supposed to be manipulated outside the microorganism and then reintroduced?
c) In Claim 25, the term "low" is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

Clarification on all of the above points is required.

17. Claims 45 and 47-49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 45, selected DNAs must be disrupted or made defective in any *Streptomyces*; however, the listed SEQ ID NOs are only found in *S. clavuligerus*.

18. Claims 31, 33, and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The term "free of any 5S clavam" is unclear. The instant specification provides no means of assessing the purity of the clavam product. Moreover, "free" is a relative term, which must be defined according to a means of assessment because a more sensitive assay may find very low levels of 5S clavam impurities. In other words, 5S impurities might not be found in an HPLC assay (using UV absorption) for detection but could easily be found, in low levels, in a mass spectrometry assay (measuring atoms directly). This is particularly problematic because this art has a long-standing history wherein purity was assessed rather crudely in the 1970's while presently highly sensitive, atomic-level assays are more routine. Clarification of the term is required.

19. Claims 45-49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 45, selected DNAs must be disrupted or made defective in any *Streptomyces*; included in these selected DNAs are degenerate variants of SEQ ID NOs specifically found in *S. clavuligerus*. Thus, it is confusing how the method steps could be carried out with genes other than those in *S. clavuligerus* since these genes would not be endogenous. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 45-49 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The general description of the specification does not describe using disrupted orfup3, -2, -1, orfdwn1, -2, and –3 specifically, but merely describe these genes generically. The Examples on pages 7-12 describe how mutants with disrupted orfup1, orfdwn1, orfdwn2, and orfdwn3 produce clavulanic acid; no support is found for disrupting orfup2 or orfup3 in S. clavuligerus to produce clavulanic acid as originally filed. Additionally, the concept of degenerate variants is not presented in the specification as originally filed in any way. Thus, these optional genes for disruption also are considered new matter.

21. Claims 30-32 and 35-36 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 is drawn to DNA that is claimed solely by function (albeit unclear function) and without any structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could

predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, 6 genes are described as being somehow involved in clavam biosynthesis such that when some of these genes are disrupted, clavulanic acid is produced in the absence of clavam-2-carboxylate, 2-hydroxymethylclavam and/or alanyl clavam. These genes are only described according to the functional characteristics of the enzymes they encode; no structural relationship is described or used in the claims. Moreover, no specific function, i.e., catalyzing a reaction in clavulanic acid biosynthesis that produces a particular, unwanted side-product, is disclosed. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure.

Claim Rejections - 35 U.S.C. § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

22. Claim 30 is rejected under 35 U.S.C. § 101, utility, because the claimed invention is directed to non-statutory subject matter. Claim 30, as written, does not sufficiently distinguish over clavulanic acid as it is naturally found in host cells that produce it because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S.

303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of "isolated" or "purified" as taught by the specification. See M.P.E.P. § 2105.

Claims 31-36 and 45-49 incorporate some limitation to distinguish clavulanic acid from that which naturally occurs by limiting the composition possible to read on the claim (the "free from" limitations).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 30-36 and 45-49 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fleming *et al.* (USPN 4,367,175). The instant claims are drawn to clavulanic acid optionally that is free from clavam-2-carboxylate, 2-hydroxymethylclavam, and 2-3(3-alanyl)clavam, or optionally as a potassium salt or optionally in combination with amoxycillin; while numerous limitations are in the claims to describe the process by which this claimed product can be obtained, this same product, even having been obtained by other means, still anticipates the claimed invention.

Fleming *et al.* teach methods of purifying clavulanic acid from fermentation of *S. clavuligerus* (see columns 12-16); said purification includes a charcoal column followed by extractions with butan-1-ol, 72% aqueous phenol/N,N-dimethylaniline/carbon tetrachloride, and barium sulphate. The final product was then tested using optical rotation, UV spectrum, IR

spectrum, NMR spectrum, TLC, and paper ionophoresis (see columns 14-15) as well as elemental analysis for the potassium salt (see column 18); particularly the IR, NMR, and elemental analysis showed no signs of impurities. Fleming *et al.* also teach the combination of purified clavulanic acid with amoxycillin (see column 2, line 57).

24. Claims 30-34 and 45-47 are rejected under 35 U.S.C. § 102(b) as being anticipated by Woroniecki *et al.* (USPN 5,130,241). The instant claims are drawn to clavulanic acid that is free from clavam-2-carboxylate, 2-hydroxymethylclavam, and 2-3(3-alanyl)clavam, optionally as a potassium salt.

Woroniecki *et al.* teach the production of clavulanic acid (compound A) from Z-(2S,5S)-3-(β-aminoethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid (compound I) using a partially purified cell extract from *S. clavuligerus* (see column 35, Example 34). As evidenced by Example 33, all compound I is converted to compound A, clavulanic acid, in this procedure. Due to the enzyme purification steps of ammonium precipitation, pellet suspension, and dialysis, no small molecule impurities from the *S. clavuligerus* are retained. Thus, the product is free of clavam-2-carboxylate, 2-hydroxymethylclavam, and 2-3(3-alanyl)clavam. Woroniecki *et al.* also describe potassium salts of their products (see column 2).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. Claims 35, 36, 48, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woroniecki *et al*. (USPN 5,130,241) in view of Fleming *et al*. (USPN 4,367,175). The instant claims are drawn to clavulanic acid that is free from clavam-2-carboxylate, 2-hydroxymethylclavam, and 2-3(3-alanyl)clavam, in combination with amoxycillin.

Woroniecki *et al*. teach as described above. While Woroniecki *et al*. teach the usefulness of clavulanic acid in combination with β-lactam antibiotics, they do not propose such a combination.

Fleming *et al*. teach combining purified clavulanic acid with amoxycillin as noted above.

It would have been obvious at the time of the invention to one of ordinary skill in the art to combine the above teachings as make pure clavulanic acid combined with amoxycillin because of the well-known protective effective of clavulanic acid against β-lactamase degradation of β-lactam antibiotics (see both Woroniecki *et al*. and Fleming *et al*.). One would have been motivated to combine the above teachings and make the invention due to the well-known pharmaceutical effectiveness of β-lactam antibiotics in the absence of degradation (see Fleming *et al*.).

Conclusion

26. Claims 30-36 and 45-49 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

February 11, 2004